Doc Code: AP.PRE.REQ

PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number (Optional) FISHMAN=19B
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 14550, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on _____ Signature _____ Typed or printed name _____	Application Number 10/565,238	Filed January 19, 2006
	First Named Inventor Pnina FISHMAN et al.	
	Art Unit 1657	Examiner S.K. Singh

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney of record.
Registration number 25,618.

☐ attorney or agent acting under 37 CFR 1.34.

Registration number if acting under 37 CFR 1.34 _____

/rlb/
Signature

Roger L. Browdy
Typed or Printed Name

202-628-5197
Telephone number

March 19, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

REASONS WHY REVIEW IS REQUESTED

The sole rejection appearing in this case is one of obviousness of all of the present claims. The present claim set includes two independent claims, claims 15 and claim 22. It is requested that these two claim sets be independently considered; they will be separately argued herein.

Claim 22 and those claims dependent therefrom are directed to a method for determining the probability that a selected subject in an inflammatory state that is the result of an autoimmune disease will respond to anti-inflammatory therapeutic treatment by means of an A_3 adenosine receptor (A_3AR) agonist. This claim is clearly not a method of diagnosis. The preamble posits that the starting subject is one that is already known to be in an inflammatory state that is the result of an autoimmune disease, such as rheumatoid arthritis (see claim 25). It is extremely important to understand that the crux of the present invention is neither diagnosis nor treatment. It is directed to that very important field of medicine relating to the determination of whether any given individual patient will benefit from a given course of therapy. It is of very important medical value to know whether a given individual is more or less likely to be susceptible to successful treatment by a given course of therapy.

In claim 22, a selected patient, who is in an inflammatory state that is the result of an autoimmune disease, is subjected to the specified procedure of the two determining steps. In this procedure, the level of expression of A_3AR in a sample of white blood cells of the subject is determined. If that level is above a predefined threshold that is above the level of A_3AR expression in white blood cells of a healthy subject, it is determined that there is a greater probability that the subject will respond to the antiinflammatory therapeutic treatment involving administration of an A_3AR agonist..

In the rejection of record, the examiner cites no reference that relates to this important field of determining whether a given subject known to have a disease will be susceptible to successful treatment by a given drug therapy. The primary reference cited by the

examiner, Gessi, is directed to a diagnostic method. The present invention is not a diagnostic method. The Gessi reference is a method of diagnosing whether a given individual has colorectal cancer by determining if there is a level of expression of A_3AR in a sample of white blood cells from that individual that is above a predetermined threshold. While the step of determining the level of A_3AR expression on white blood cells is the same as that used in the present invention, it is done for a completely different purpose and is done to completely different individuals. Gessi does it to diagnose colorectal cancer. The present invention diagnoses nothing and has nothing whatsoever to do with colorectal cancer. The patient that is subjected to the present process is one who has already been diagnosed as having an autoimmune disease that results in inflammation. While a step of determining the level of A_3AR expression in white blood cells is utilized, the second determining step of claim 22 is nowhere taught or suggested by Gessi and is in no way related to the manner in which the information as to A_3AR expression in white blood cells is used by Gessi. Furthermore, the subject whose white blood cells are examined is a totally different subject than that in the Gessi diagnostic process. There would be no reason for anyone reading Gessi to start with an individual known to have an autoimmune disease resulting in inflammation.

The Rhodes reference is cited by the examiner as teaching that there is inflammation involved in colorectal cancer. This fact is not disputed, but neither can the examiner dispute that colorectal cancer is not an autoimmune disease.

The examiner cited Fishman for the known use of A_3AR agonists, such a IB-MECA, for the treatment of inflammation. Of course, this fact is conceded as the present invention in an improvement thereon arising out of the same laboratory that produced the Fishman et al. publication. It is well known that A_3AR agonists are within the arsenal of possible drug treatments of inflammation caused by autoimmune diseases. However, the present invention is directed at selecting those specific individuals who are most likely to respond to such a treatment. Gessi does not suggest that the measurement of A_3AR expression in white blood cells will provide any clue to which patients that have already been diagnosed with any

condition (let alone an autoimmune disease that results in inflammation) will respond to treatment by means of an A_3AR agonist.

The only remaining reference is Montesinos. The examiner states that Montesinos discloses the role of A_3AR receptors, the activation of which is required for the inhibition of inflammation by methotrexate, commonly used for the therapy of chronic inflammatory diseases, including autoimmune joint disorders, such as RA. The conclusion set forth at the end of the abstract of Montesinos is that adenosine, acting at A_{2A} and A_3 receptors, is a potent regulator of inflammation. Accordingly, this supplies no more information than has already been supplied by the Fishman reference, which discloses that an A_3AR agonist may be used in the treatment of RA. It certainly does not suggest, either alone or in combination with any of the other references of record, that the degree of expression of the A_3AR receptor on white blood cells of patients having an autoimmune disease that results in inflammation will be a predictor of successful treatment with an A_3AR agonist. That is the crux of the present invention and that is nowhere taught or suggested by any of the references of record.

The examiner has done no more than to search the prior art in a concerted hindsight reconstruction of the present invention in an attempt to provide an explanation why the present invention works. First, the examiner has failed in this attempt. Second, this is an improper approach to determination of obviousness. As stated in *Ex parte Levengood*, 28 USPQ 2d 1300, 1301-1302 (BPAI 1993):

> In this case, however, the only suggestion for the examiner's combination of the isolated teachings of the applied references improperly stems from appellant's disclosure and not from the applied prior art. … That one can reconstruct and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the references to make the claimed invention.

The U.S. Supreme Court is substantially in accordance with the Board's reasoning in *Levengood,* quoted above, as is evidenced by *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). Note where the court, 127 S.Ct at 1742, stated:

> A fact finder should be aware of, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.

Note also where the court, 127 S. Ct. at 1741, cited with approval the following statement from *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006):

> Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with rational underpinning to support the legal conclusion of obviousness.

Here, the examiner has not and cannot provide articulated reasoning with rational underpinning to support the legal conclusion that those of ordinary skill in the art at the time the present invention was made would have found it obvious that the appearance of an increased level of expression of A_3AR on white blood cells in a patient known to have an autoimmune disease that results in inflammation would be a predictor of a higher probability of successful treatment with an A_3AR agonist than would the appearance of a normal level of A_3AR expression.

In conclusion, it is apparent that there is nothing in Rhodes, Fishman or Montesinos that would motivate one of ordinary skill in the art to substitute as the starting patient in Gessi, a person that has already been diagnosed with an autoimmune disease that results in inflammation. Furthermore, it is also apparent that there is nothing in Gessi, Rhodes, Fishman or Montesinos that would motivate one of ordinary skill in the art to use the result of a test for the level of expression of A_3AR in white blood cells in such a patient as a determining factor with respect to the probability that the patient will respond to treatment with an A_3AR agonist. Accordingly, the present invention as a whole as defined in claim 22 and those claims dependent therefrom could not have been obvious to those of ordinary skill in the art in the sense

required by 35 USC 103(a). Reversal of the examiner and withdrawal of this rejection is therefore respectfully urged.

The same arguments discussed above with respect to claim 22 and those claims dependent therefrom are also applicable to independent claim 15 and those claims dependent therefrom. Claim 15 is directed to a method for selecting a subject in an inflammatory state that is the result of an autoimmune disease, which subject is suitable for antiinflammatory therapeutic treatment by means of an A_3AR agonist. The subject is selected as being suitable to receive such treatment if the level of expression of A_3AR in a sample of the white blood cells of that subject is above a predetermined threshold that is above the level of A_3AR expression in white blood cells of a healthy subject. This claim is effectively claiming the same thing as discussed above with respect to claim 22, but simply using slightly different language. The language "selecting a subject in an inflammatory state that is the result of an autoimmune disease, which subject is suitable for antiinflammatory therapeutic treatment by means of an A_3AR agonist," means that the starting subject is already known to be in an inflammatory state that is the result of an autoimmune disease and that a selection is being made among those subjects already known to have an inflammatory state that is the result of an autoimmune disease, to find those suitable for treatment with an A_3AR agonist. This claim does not read on a method of diagnosis. Accordingly, it free of the prior art for the same reasons as discussed above with respect to claim 22 and those claims dependent therefrom.

Accordingly, reversal of the examiner and allowance of claim 15 and those claims dependent therefrom are also respectfully urged for the same reasons as discussed above with respect to claim 22 and its progeny.